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EXAMINER	
CURTIS Joseph Curtis	
ART UNIT	**PAPER NUMBER**
1812	4

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1812

DATE MAILED: 04/19/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on September 19, 95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), -0- days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

→ Substitute

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 5-7 and 21-26 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.

3. ☒ Claims 5 and 6 are allowed.

4. ☒ Claims 7, 21-26 are rejected.

5. ☒ Claims 6, 22-24 are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).

12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.

13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

Part III DETAILED ACTION

Election/Restriction

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 5-7, and 21-26 drawn to H4-1BB receptor proteins, and a pharmaceutical composition classified in Classes 530 and 514, subclasses 350 and 2 respecitvely.

II. Claims 19 and 20, drawn to a process for preparing recombinant DNA molecules encoding H4-1BB receptor proteins, classified in Class 435, subclass 69.1.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (M.P.E.P. § 806.05(f)). In the instant case the product as claimed can be made a materially different process such as organic synthesis.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by the different classification, restriction for examination purposes as indicated is proper.

2. During a telephone conversation with Christopher Michaels on 3/14/96 a provisional election was made with traverse to prosecute the invention of Group I, the H4-1BB receptor proteins, claims 5-7 and 21-26. Affirmation of this election must be made by applicant in responding to this Office action. Claims 19 and 20 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to non-elected inventions.

The disclosure is objected to because of the following informalities: the status of all applications to which cross reference is made at the beginning of the specification should be updated. Appropriate correction is required.

Claim Objections

3. The specification is not in compliance 37CFR 1.821 because it fails to recite a SEQ ID NO: at each and every disclosure of the sequence, see pages 11, 15 and 16.

a. Claim 6 is objected to as failing to comply with the sequence rules 37 CFR 1.821(d) because of the following informalities: The amino acid sequence corresponding to figure 2 should be referred to by SEQ ID NO:2. The SEQ ID NO:1 cited in claims 22, 23 and 24 should read as SEQ ID NO:2. Appropriate correction is required.

b. Claims 22, 23, and 24 are objected to because of the following informalities: The amino acid sequences recited in the claims denoting SEQ ID NO:1, should correspond to SEQ ID NO:2,

which denotes the amino acid sequence of the peptides.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 7 and 21, 23-24 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited in scope to the protein represented by the SEQ ID NO:2. See M.P.E.P. §§ 706.03(n) and 706.03(z).

4a. Claim 7 recites a H4-1BB receptor protein and fragments and derivatives. The murine form of the H4-1BB receptor and its ligand is known in the art. However, the specification fails to provide an adequate written description, or teachings of enablement, of fragments and derivatives of the H4-1BB receptor amino acid sequence which are capable of being used as a probe to identify potential ligands. The specification fails to provide an adequate written description as to what amino acid sequences are necessary to make a probe that can be used to isolate ligands. The specification fails to disclose identifiable characteristics of a ligand. Furthermore, the ligand

binding domain of H4-1BB has not been described or identified in the specification. The murine form of the receptor 4-1BB shares structural similarity to members of the (tumor necrosis factor/low affinity nerve growth factor) TNF/NGF receptor superfamily. If probes derived from the H4-1BB amino acid sequence bound NGF or TNF would they be considered as candidate ligands for the instant receptor? Without describing any kinetic characteristics or ligand antagonist profiles it would be very difficult to define what a ligand is or how to block its binding. In view of the above, it is the Examiners position that one skilled in the art could not make and/or use the invention without undue experimentation.

4b. Claim 21 recites a H4-1BB protein comprising 12 amino acids: Leu-Gln-Asp-Pro-Cys-Ser-Asn-Cys-Pro-Ala-Gly-Thr at the N-terminal. It is possible to obtain polypeptides possessing this sequence that display a wide range of biological activity not mentioned in the specification. It is unpredictable what result you will expect. The claim is broad and reads on any protein of any sequence length and amino acid composition after those cited. The specification did not provide guidance or working examples on how to make, use and purify all the possible proteins beginning with this sequence. The biological significance of this N-terminal sequence is absent from the disclosure and a demonstration that its activity is restricted exclusively to H4-1BB receptors is uncertain. In view of the above, it is the

Examiners position that one skilled in the art could not make and/or use the invention without undue experimentation.

4c. Claim 23 recites H4-1BB proteins encoded by the amino acids 24-255 and 24-186 of SEQ ID NO:2, except for conservative amino acid substitutions. The specification fails to provide an adequate written description, or teachings of enablement, of the conservative amino acid substitutions within the amino acid sequence corresponding to SEQ ID NO:1. The amino acids determined to be essential in this matter were not identified and no functional biological significance was attributed to either set of amino acids noted as 24-186 and 24-255 of SEQ ID NO:1. The corresponding proteins are approxamately 162 and 231 amino acids in length. Considering there are 20 different amino acids, the number of H4-1BB analogs produced by a single amino acid substitution corresponds to 3240 and 4620 different receptors, respectively. Additionally, each set of amino acids noted could contain a portion of the receptor that is conserved throughout the superfamily. If this were true, without further clarification as to the significance of these amino acids one would not be able to determine the meets and bounds of the claimed invention over the other members of the receptor superfamily. In view of the above, it is the Examiners position that one skilled in the art could not make and/or use the invention without undue experimentation.

4d. Claim 24 is recites a H4-1BB proteins encoded by the amino acids 24-255 and 24-186 of SEQ ID NO:1. The claim contains open language "comprises" and the specification fails to provide an adequate written description, or teachings of enablement, of fragments capable of binding a 4-1BB ligand. The specification did not disclose which amino acids in the extracellular portion of the receptor are required for ligand binding. The absence of an identified ligand presents a practical problem in that without it efforts to define the ligand binding domain would result in extensive experimentation. Secondly, the specification did not discuss any features common to the extracellular domains of the murine and human forms of the 4-1BB receptor. The specification provides a 65% sequence identity between the two, but where the identity lies was not elaborated on. If the sequence identity resides exclusively throughout the extracellular domain, a 35% sequence disparity remains and may exert a functional effect on the binding of any potenitial ligands. Attempts to identify ligands capable of binding to extracellular domains from two proteins with that much disparity would produce unpredictable results. The specification did not provide any guidance on how to overcome this disparity in receptor structure and did not provide any working examples of fragments derived from H4-1BB that were capable of binding murine 4-1BB ligands. In view of the above, it is the Examiners position that one skilled in the art

could not make and/or use the invention without undue experimentation.

4e. Claims 25 and 26 recite pharmaceutical compositions of soluble H4-1BB and admixtures of diluents carriers, or excipients. Pharmaceutical compositions consisting of secreted forms of lymphocytic proteins are common in the art, but exclude any mention of the claimed invention. The specification does not provide guidance on how to make pharmaceutical compositions containing soluble H4-1BB and does not provide any working examples. The specification does not teach how to determine an effective amount of a pharmaceutical composition. It is unclear what disease is being treated with these compositions. The specification did not describe any pathology associated with the 4-1BB receptors in the mouse or in humans. Therapeutic value was not asserted in the specification and no examples of concentrations demonstrating effective alteration of T cell function was presented as a working example of therapeutic effect. Therefore, it would be difficult to predict the therapeutic value of 4-1BB ligands. In view of the above, it is the Examiners position that one skilled in the art could not make and/or use the invention without undue experimentation.

5. Claim 20, 25 and 26 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 20 and 24 are ambiguous in the recitation "capable of", if the fragment binds the ligand, replacing "capable of binding" with --that binds-- is suggested. It has been held that the recitation that an element is "capable of" performing a function is not a positive limitation but only requires the ability to so perform. It does not consittute a limitation in any patentable sense. *In re Hutchinson*, 69 USPQ 138. Claims 25 and 26 are vague and indefinite because they use the phrase "effective amount" without stating what effect is to be achieved.

6. Claim 7 is rejected under 35 U.S.C. § 112, fourth paragraph, as being of improper dependent form for failing to further limit the subject matter of a previous claim. The test as to whether a claim is a proper dependent claim is that it shall include every limitation of the claim from which it depends. Claim 7 includes undisclosed "fragments and derivatives of thereof" that are not disclosed in the preceeding claim.

Allowable Subject Matter

9. Claims 5 and 6 are free of the prior art of record.

10. Claim 6 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

11. As allowable subject matter has been indicated, applicant's response must either comply with all formal requirements or specifically traverse each requirement not complied with. See 37 CFR 1.111(b) and MPEP § 707.07(a).

Conclusion

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph

Curtis whose telephone number is (703) 305-6571. The examiner can normally be reached on Monday thru Friday from 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Garnette Draper, can be reached on (703) 308-4232. The fax phone number for this Group is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-1235.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

GARNETTE D. DRAPER
SUPERVISORY PRIMARY EXAMINER
GROUP 1800

Joseph Curtis Ph.D
Patent Examiner
March 29, 1996